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Comparison of quetiapine immediate- and extended-release formulations for bipolar depression: A systematic review and network meta-analysis of double-blind, randomized placebo-controlled trials

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ABSTRACT

This study evaluated the efficacy and safety/tolerability of quetiapine extended-release 300 mg/day (QUEXR300), quetiapine immediate-release 600 mg/day (QUEIR600), and quetiapine immediate-release 300 mg/day (QUEIR300) formulations for treating bipolar depression. A random-effect network meta-analysis of 8-week, double-blind, randomized placebo-controlled trials was used to determine the most optimal agent for intervention. Remission rate was set as the primary outcome. Secondary outcomes were response rate, improvement in the Montgomery–Åsberg Depression Rating Scale score, discontinuation rate, and the incidence of individual adverse events. Seven eligible studies including 3267 participants were included in the meta-analysis. The QUEIR600, QUEIR300, and QUEXR300 groups were superior to the placebo group in every efficacy outcome; however, there were no significant differences in the efficacy outcomes among the treatment groups. All treatment groups exhibited higher incidences of extrapyramidal symptoms, dry mouth, somnolence, constipation, and increase in body weight than the placebo group. The QUEIR600 and QUEIR300 groups had higher incidences of dizziness than the placebo group. The QUEIR600 group had a higher discontinuation rate due to adverse events than the placebo group, and the QUEIR300 group had higher blood HbA1c levels than the placebo group. The QUEIR600 and QUEXR300 groups had higher incidences of ≥7% weight gain than the placebo group. The QUEXR300 group had a higher incidence of fatigue than the QURIR300 and placebo groups. In conclusion, there were no significant differences in the efficacies of QUEIR600, QUEIR300, and QUEXR300 in treating bipolar depression; moreover, tolerance to QUEIR600 might be worse than the other treatments.

1. Introduction

Bipolar disorder is a common mood disorder characterized by alternating manic and depressive episodes (Grande et al., 2016) and a high relapse rate (Grande et al., 2016). A recent systematic review reported that patients with bipolar depression area at a 20–30-fold increased risk of suicide than the general population (Pompili et al., 2013). Furthermore, a recent, five-year cohort study reported that the incidence of suicide increases 5-fold during subthreshold depression and 25-fold during major depressive episodes compared with that during euthymic phases (Holma et al., 2014).

The recent three-treatment guidelines for bipolar depression recommend both pharmacological treatment including antipsychotics or mood stabilizers and nonpharmacological treatments such as psychotherapy (Fountoulakis et al., 2017; Goodwin et al., 2016; Yatham et al., 2018). Quetiapine is a commonly recommended first-line drug for bipolar depression (Fountoulakis et al., 2017; Goodwin et al., 2016; Yatham et al., 2018). It is a dopamine D_2 and serotonin $5HT_{2A}$receptor antagonist with higher affinity for 5-HT_{2A} receptors than D_2 receptors. It also has affinities for dopamine D_1, serotonin 5-HT_{1A}, histamine H_1, and adrenaline α_{1b} and α_2 receptors (FDA, 2009). Furthermore, norquetiapine, an active metabolite of quetiapine, has a high affinity for norepinephrine transporters and is a partial agonist of serotonin 5-HT_{1A} receptors (FDA, 2009). Quetiapine is available as extended-release (QUEXR) and immediate-release (QUEIR) formulations. QUEXR is characterized by sustained drug release with one dose/day and faster dose titration than QUEIR, which has to be administered twice daily and over a longer dose titration period (FDA, 2009).

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It is currently uncertain whether QUEXR is superior to QUEIR regarding treatment efficacy or safety/tolerability outcomes for bipolar depression. To the best of our knowledge, only one double-blind, randomized, head-to-head comparison study assessing QUEXR and QUEIR for bipolar depression has been published (Riesenberg et al., 2012). This study evaluated differences in the profiles of initial safety outcomes of 139 patients with bipolar depression who were administered QUEXR or QUEIR as escalating doses of 50, 100, 200, and 300 mg once daily in the evening from day 2 to day 6. The study demonstrated that after 1–3 h after treatment administration, QUEXR exhibited lower sedation intensity than QUEIR. There were no differences in other safety outcomes. However, the study limitations include its short duration, which implied that the occurrence of adverse events that often occur after several weeks of drug administration (e.g., weight gain) was not assessed. Moreover, the study population was small, implying insufficient statistical power to detect significant differences in some safety outcomes between the groups. Finally, the study did not investigate differences in treatment efficacy between the groups. The objective of the present study was to evaluate the currently available evidence regarding relative efficacy and safety/tolerability of QUEXR and QUEIR for the treatment of bipolar depression.

A network meta-analysis is a statistical technique that facilitates both the direct and indirect comparisons of interventions even if they were not directly compared in the original study (Cochrane, 2011; Salanti et al., 2008). Till date, four double-blind, placebo-controlled trials of QUEIR [fixed-dose 600 mg/day (QUEIR600) and fixed-dose 300 mg/day (QUEIR300)] (Calabrese et al., 2005; McElroy et al., 2010; Thase et al., 2006; Young et al., 2010), and three double-blind, placebo-controlled trials of QUEXR [fixed-dose 300 mg/day (QUEXR300)] (Li et al., 2016; Murasaki et al., 2018; Suppes et al., 2010) have been conducted. We conducted a network meta-analysis of these trials to examine differences in the treatment efficacy and safety/tolerability outcomes of QUEIR600, QUEIR300, and QUEXR300 for bipolar depression.

2. Material and methods

The present meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009) (**PRISMA checklist**) and is registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/. CRD42019127123).

2.1. Inclusion criteria, search strategy, data extraction, and outcomes

A systematic literature review was performed according to the patients, interventions, comparisons, and outcome strategies. Patients with bipolar depression who were not being treated with any mood stabilizers or antipsychotics at the baseline were eligible. The intervention groups were administered fixed-dose QUEIR or QUEXR, and the control group was administered placebo. The outcomes were efficacy and safety/tolerability (detailed information in the following section). Only double-blind, randomized, placebo-controlled trials with interventions of ≥2 weeks were included. Three authors (T.K., K.S., and Y.M.) independently identified eligible studies indexed in the Scopus, MEDLINE, and the Cochrane library databases and published in any language from the inception of the study to January 6, 2019. The search terms included (bipolar) AND (depress*) AND (random*) AND (placebo) AND (double-blind) AND (quetiapine). The authors also searched ClinicalTrials.gov (http://clinicaltrials.gov/) and the International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) to ensure a comprehensive search and minimize publication bias. The reference lists of the retrieved publications were searched for additional relevant published and unpublished studies, including conference abstracts.

2.2. Data synthesis

Three authors (T.K., K.S., and Y.M.) extracted data from the articles and entered the data into Review Manager 5 software (RevMan, 2014). Initially, the study design, patient, and treatment characteristics of the studies to be included in the current meta-analysis were reviewed. The primary outcome of remission rate was defined using a Montgomery-Åsberg Depression Rating Scale (MADRS) score of ≥12 (Montgomery and Asberg, 1979). The secondary outcomes included response rate (≥50% reduction in the MADRS score at the endpoint from that at the baseline), an improvement of the MADRS score from the baseline, all-cause discontinuation, discontinuation due to adverse events, and individual adverse events. Intention-to-treat, modified intention-to-treat, or full-analysis set population data were used in the analysis. The algebraic signs of the values of blood high-density lipid (HDL) cholesterol were reversed as decreased blood HDL cholesterol values indicate increased impairment.

2.3. Statistical analysis

Only outcomes with available data from at least two of the three treatment groups (QUEIR600, QUEIR300, or QUEXR300) were included in the meta-analysis. Four categorical pairwise meta-analyses (QUEIR600 vs. placebo, QUEIR300 vs. placebo, QUEIR600 vs. QUEIR300, and QUEXR300 vs. placebo) were performed. The pairwise meta-analyses was performed using the Review Manager 5 software (RevMan, 2014). A random-effects model was used to account for potential heterogeneity across the included trials (Higgins and Green, 2011). Dichotomous outcomes were reported as risk ratios (RRs) with 95% confidence intervals. Continuous outcomes were analyzed using the mean differences (MDs) between the treatment groups. If standard deviation (SD) values were not available, SD values from similar studies (with same quetiapine formulation and dose) were used (Higgins and Green, 2011). If intergroup differences in treatment efficacy or adverse events based on RRs were significant, the number needed to treat or harm was calculated from the risk difference. Study heterogeneity was assessed using I^2 statistics, with an $I^2 \geq 50\%$ indicating considerable heterogeneity (Higgins and Green, 2011). However, our pairwise meta-analysis of the primary outcome did not demonstrate considerable heterogeneity.

Using random-effects models (DerSimonian and Laird, 1986), a Bayesian network meta-analysis was conducted using the GeMTC package in the R Statistics software (van Valkenhoef et al., 2012). Direct and indirect evidences from the included studies were integrated using a Bayesian network meta-analysis, and the estimates of maximum power were provided (Salanti et al., 2008). MDs and RRs and their 95% credible intervals were calculated for continuous and dichotomous data, respectively. The Markov chain Monte Carlo method was used to obtain pooled estimates of effect size in the Bayesian approach (van Valkenhoef et al., 2012). The GeMTC package automatically sets the prior distributions. The number of burn-in iterations, the number of interface iterations, and thinning factor were set at 5000, 20,000, and 10, respectively. Convergence was assessed using the Brooks–Gelman–Rubin diagnostic (Brooks and Gelman, 1998), which compares within-chain and between-chain estimates to diagnose whether the simulation has reached a stable state. The values of < 1.05 are generally considered safe (van Valkenhoef et al., 2012). Our network meta-analysis approaches were based on a consistency model. The deviance information criterion to provide a measure of model fit, which accounts for model complexity, was calculated (Dias et al., 2010). The random-effects SD (i.e., heterogeneity SD) was used as a measured of heterogeneity (van Valkenhoef et al., 2012). Heterogeneity can be compared with the important effect sizes observed in the network, and if it is greater than or comparable to these size effects, then the findings may not be valid (van Valkenhoef et al., 2012). The data available for the meta-analysis were not sufficient to perform node-splitting to assess

inconsistencies within the intervention network (Dias et al., 2010). The relative effect estimates calculated using the Bayesian approach were used to estimate the probability that one treatment was superior to the other. The Bayesian analyses also estimated rank probabilities, i.e., the probability of each treatment obtaining each possible rank as shown by their relative effects (outcome value) (van Valkenhoef et al., 2012). The primary outcome might have been influenced by differences in the placebo responses reported in the included trials (Iovieno et al., 2016). A meta-regression analysis was performed to evaluate the association between the meta-analysis results for the primary outcome and the percentage of placebo responders. We performed both pairwise and network meta-analysis; however, as a network meta-analysis can avoid some limitations of a pairwise meta-analysis, we primarily discussed the results of the network meta-analysis in this study. A funnel plot was used to assess potential publication bias although the Cochrane Handbook recommends its use only if ten or more studies are included in the meta-analysis (Higgins and Green, 2011).

3. Results

3.1. Study characteristics

Of the 311 retrieved publications, 69 duplicates and 242 publications based on an abstract/title review were excluded; moreover, four articles were excluded after a full-text review (Citrome et al., 2014; Ketter et al., 2014; Sanford and Keating, 2012) and another because it was a short-duration study (Riesenberg et al., 2012)] (Supplementary Fig. 1). No additional studies were retrieved from the clinical trial registries. Finally, seven fixed-dose studies including 3267 participants were included in the meta-analysis (Calabrese et al., 2005; Li et al., 2016; McElroy et al., 2010; Murasaki et al., 2018; Suppes et al., 2010; Thase et al., 2006; Young et al., 2010). The groups assessed were QUEIR600 (n = 864), QUEIR300 (n = 863), QUEXR300 (n = 467), and placebo (n = 1073). The mean age of the study participants was 38.6 years; 41.5% were men. The characteristics of the included studies are shown in Table 1. All studies were 8-week, double-blind, randomized, placebo-controlled trials sponsored by pharmaceutical companies and were published in English. The methodological quality of all seven trials was high as assessed with the Cochrane Risk of Bias Tool (Supplementary Fig. 2). The results of both the pairwise meta-analysis and the network meta-analysis are shown in the Supplementary appendix 1–22.

3.2. Pairwise meta-analysis

3.2.1. Efficacy outcomes

All the efficacy outcomes reported in the QUEIR600, QUEIR300, and QUEXR300 groups were superior to those in the placebo group (Table 2). There were no significant differences in any of the efficacy outcomes reported in the QUEIR600 and QUEIR300 groups (Table 2).

3.2.2. Safety/tolerability outcomes

Safety and tolerability outcomes are shown in Table 3. The risk of discontinuation due to adverse events, extrapyramidal symptoms, dry mouth, dizziness, somnolence, fatigue, constipation, ≥7% weight gain, increased body weight, and increased blood HbA1c level) were compared between the QUEIR600 and placebo groups. The QUEIR600 group exhibited a higher risk of discontinuation due to adverse events and increased body weight than the QUEIR300 group. However, the QUEIR600 group was associated with a lower incidence of treatment-emergent mania than the placebo group. The risk of extrapyramidal symptoms, dry mouth, dizziness, somnolence, constipation, ≥7% weight gain, increased body weight, and increased blood HbA1c levels were greater in the QUEIR300 group that in the placebo group. The risk of extrapyramidal symptoms, dry mouth, dizziness, somnolence, fatigue, constipation, ≥7% weight gain, and increased body weight was greater in the QUEXR300 group than that in the placebo group.

3.3. Network meta-analysis

3.3.1. Efficacy outcomes

In the comparisons of QUEIR600 vs. placebo, QUEIR300 vs. placebo, QUEXR300 vs. placebo, and QUEIR600 vs. QUEIR300 for efficacy outcomes, the results of the network meta-analysis and pairwise meta-analysis were slightly similar (Table 2). There were no significant differences in any efficacy outcome between the QUEXR300 and QUEIR600 groups or between the QUEXR300 and QUEIR300 groups (Table 2). There was no considerable heterogeneity among the results of the primary outcome of the network meta-analysis (Supplementary appendix 1). The funnel plot of the primary outcome was symmetrical, suggesting that there was no significant publication bias (Supplementary appendix 1). The meta-regression analysis did not demonstrate any significant association of effect size with remission rate and the percentage of placebo responders (Supplementary appendix 1).

3.3.2. Safety/tolerability outcomes

In the comparisons of QUEIR600 vs. placebo, QUEIR300 vs. placebo, QUEXR300 vs. placebo, and QUEIR600 vs. QUEIR300 for safety/tolerability outcomes, the results of the network meta-analysis were similar to the results of the pairwise meta-analysis (Table 3). Although there were not any differences in safety/tolerability outcomes between QUEXR300 and QUEIR600 (Table 3), the QUEXR300 group was associated with an increased incidence of fatigue compared with the QUEIR300 group (Table 3).

4. Discussion

To the best of our knowledge, this is the first network meta-analysis assessing the efficacy and safety/tolerability of quetiapine for the treatment of bipolar depression. No significant differences were noted between the treatment efficacies of QUEXR300 and QUEIR600 or QUEXR300 and QUEIR300. The risks of some individual adverse events, such as extrapyramidal symptoms, dry mouth, somnolence, constipation, and increased body weight were greater in the QUEXR300, QUEIR600, and QUEIR300 groups than those in the placebo group. The incidence of discontinuation due to adverse events was greater in the QUEIR600 group than that in the placebo group. These results suggest that in patients with bipolar depression, QUEIR600 may be inferior to QUEIR300 and QUEXR300 in terms of tolerability. QUEXR300 did not influence blood HbA1c levels; however, QUEIR300 increased HbA1c levels compared with placebo. The meta-analysis found that differences of the QUEXR and QUEIR formulations may influence glucose metabolism; however, no differences in other metabolic outcomes were detected between the QUEXR and QUEIR groups. The results are in agreement with a previous systematic review that reported no dose-related weight gain following treatment with quetiapine (Simon et al., 2009). This analysis did not detect differences in any metabolic outcomes associated with QUEIR600 or QUEIR300. The QUEXR300 group was associated with an increased risk of fatigue compared with QUEIR300, possibly because QUEXR prolongs plasma levels compared with QUEIR (El-Khalili, 2012). Therefore, when prescribing QUEXR, it is necessary to appropriately adjust the dosage of the oral administration.

The risk of somnolence was greater in the QUEXR300, QUEIR600, and QUEIR300 groups than that in the placebo group. However, the network meta-analysis revealed no differences in the incidence of somnolence between the QUEXR300 and QUEIR600 groups or between the QUEXR300 and QUEIR300 groups. Compared with the placebo group though, the QUEXR300 group exhibited a trend of increased risk ratio for somnolence than the QUEIR600 and QUEIR300 groups. The network meta-analysis revealed that the heterogeneity SD value was smaller than the effect size for this outcome; however, the pairwise

Table 1
Study, patient, and treatment characteristics of the included double-blinded, randomized placebo-controlled trials of patients with bipolar depression.

(1) Study, (2) total n, (3) country, (4) sponsorship, (5) study design	(1) Diagnostic criteria (age range. y), (2) type (%), (3) analyzed population (missing data)	Drug (mg/d)	n	Age (mean ± SD, y)	Male (%)	Race (%)	Concomitant drugs (mg/d)	Efficacy outcomes[c]
(1) Calabrese et al., 2005, (2) 542, (3) USA, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV using SCID (18–65) (2) BD1 (66.4) or BD2 op with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) ITT (LOCF)	QUEIR600, fixed dose, ODB	180	37.3 ± 11.4	41.8	Caucasian 84.7	During the first 3 wk of the study, ZOL5-10 and/or LOR1-3[a]	QUEIR600 > PLA and QUE300IR > PLA: MADRS, response rate, remission rate, HAMD17, CGI-I, CGI-S, HAMA, PSQI, Q-LES-Q
		QUEIR300, fixed dose, ODB	181	36.6 ± 11.2	45.9	Caucasian 82.0		
		PLA	181	38.3 ± 11.1	37.9	Caucasian 76.3		
(1) Li et al., 2016, (2) 296, (3) China, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV-TR (18–65) (2) BD1 (50.9) or BD2 op with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) FAS (LOCF)	QUEXR300, fixed dose, ODE	148	33.4 ± 11.9	48.2	Chinese 100	none	QUEXR300 > PLA: MADRS, response rate, remission rate, HAMD17,, YMRS
		PLA	148	32.8 ± 11.0	47.9			
(1) McElroy et al., 2010, (2) 618, (3) international, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV (≥18) (2) BD1 (64.3) or BD2 pt with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) ITT (LOCF)	QUEIR600, fixed dose, ODB	247	38.5	39.2	NR	During the first 3 wk of the study, ZOL≤10, ZAL≤20, ZOP≤7.5, CHL≤1 and/or LOR1-3	QUEIR600 > PLA and QUEIR300 > PLA: MADRS, response rate, HAMD17, HAMA, CGI-BP-S QUEIR600 > PLA and QUEIR300 = PLA: remission rate QUEIR600 = PLA and QUEIR300 = PLA: CGI-BP-S, Q-LES-Q, SDS
		QUEIR300, fixed dose, ODB	245	38.4	38.4			
		PLA, fixed	126	38.7	33.1			
(1) Murasaki et al., 2018, (2) 356, (3) Japan, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV-TR (20–64) (2) BD1 (28.7) or BD2 pt with MDE (MINI, HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) FAS (LOCF)	QUEXR300, fixed dose, ODB	179	38.1 ± 11.2	48.0	Japanese 100	During the first 2 wk of the study ZOP, TRI, ESZ and/or LOR	QUEXR300 > PLA: MADRS, response rate, remission rate, HAMD17, CGI-BP-S
		PLA	177	38.8 ± 11.0	42.9			
(1) Suppes et al., 2010, (2) 280, (3) USA, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV (18–65) (2) BD1 (80.4) or BD2 op with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) mITT (LOCF)	QUEXR300, fixed dose, ODE	140	39.0 ± 11.3	33.8	NR	During the first 3 wk of the study, ZOL≤10, ZAL≤20, ZOP≤7.5, CHL≤1 and/or LOR≤2	QUEXR300 > PLA: MADRS, response rate, remission rate, CGI-BP-S
		PLA	140	39.9 ± 12.8	37.2			
(1) Thase et al., 2006, (2) 509, (3) USA, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV using SCID (18–65) (2) BD1 (66.4) or BD2 op with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) ITT (LOCF)	QUEIR600, fixed dose, ODB	169	38.2 ± 11.0	45.0	Caucasian 76.2	During the first 3 wk of the study, ZOL5-10 and/or LOR1-3[b]	QUEIR600 > PLA and QUE300IR > PLA: MADRS, response rate, remission rate, HAMD17, CGI-I, CGI-S, HAMA QUER600 > PLA and QUE300IR = PLA: SDS QUEIR600 = PLA and QUE300IR > PLA: Q-LES-Q
		QUEIR300, fixed dose, ODB	172	37.2 ± 10.5	44.5	Caucasian 69.0		
		PLA	168	37.7 ± 11.8	39.8	Caucasian 85.6		
(1) Young et al., 2010, (2) 666, (3) international, (4) industry, (5) 8w-DBRPCT	(1) DSM-IV (18–65) (2) BD1 (61.8) or BD2 op with MDE (HAMD17 ≥ 20, HAMD (item1)≥2, YMRS≤12) (3) ITT (LOCF)	QUEIR600, fixed dose, ODB	268	42.8	36.5	NR	During the first 3 wk of the study ZOL≤10, ZAL≤20, ZOP≤7.5, CHL≤1 and/or LOR1-3	QUEIR600 > PLA and QUEIR 300 > PLA: MADRS, response rate, remission rate, CGI-BP-S, HAMD17, HAMA QUEIR600 > PLA and QUER300 = PLA: SDS and MOSCS
		QUEIR300, fixed dose, ODB	265	42.3	42.7			
		PLA	133	41.5	45.7			

BD (I, II): bipolar (I, II) disorder, CGI(-BP)-I (-S): the Clinical Global Impressions(-bipolar)-Improvement (-Severity), CHL: chloral hydrate, d: day, DBRPCT: double-blind, randomized, placebo-controlled trial, DSM (-IV, -TR): Diagnostic and Statistical Manual of Mental Disorders (-Fourth Edition, -Text Revision), ESZ: eszopiclone, FAS: full analysis set, HAMA: Hamilton Anxiety Rating Scale, HAMD17: Hamilton Depression Rating Scale 17-item, (m)ITT: (modified) intention-to-treat, LOCF: last-observation-carried-forward, LOR: lorazepam, MDE: major depressive episode, n: number of patients, MINI: Mini-International Neuropsychiatric Interview, MOSCS: Medical Outcomes Study cognitive scale, NR: not report, ODB: once daily at bedside, OBE: once daily in the evening, op: outpatient, PLA: placebo, PSQI: Pittsburgh Sleep Quality Index, Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire, QUEIR(XR): quetiapine immediate release (extended release), SCID: Structured Clinical Interview for DSM-IV, SD: standard deviation, SDS: Sheehan Disability Scale, TRI: triazolam, USA: United States of America, w: week, y: year, YMRS: Young Mania Rating Scale, ZAL: zaleplon, ZOL: zolpidem, ZOP: zopiclone

[a] : LOR use during the study was 8.3%, 9.5%, and 5.6% in the PLA, QUEIR300, and QUEIR600 groups, respectively. ZOL use during the study was 8.3%, 4.5%, and 6.7% in the placebo, QUEIR300, and QUEIR600 groups, respectively.

[b] : LOR use during the study was 3.0%, 1.2%, and 3.6% in the PLA, QUEIR300, and QUEIR600 groups, respectively. ZOL use during the study was 3.0%, 1.2%, and 1.8% in the placebo, QUEIR300, and QUEIR600 groups, respectively.

[c] : Primary outcomes in each study are underlined.

Table 2
Efficacy outcomes.

Outcome	Comparison	PMA RR (95% CI)/NNT	NMA RR (95% CrI)
Remission rate	QUEIR600 vs PLA	0.69 (0.62, 0.78)/6	0.69 (0.60, 0.80)
	QUEIR300 vs PLA	0.72 (0.64, 0.80)/6	0.71 (0.62, 0.82)
	QUEIR600 vs QUEIR300	0.97 (0.86, 1.09)	0.97 (0.83, 1.12)
	QUEXR300 vs PLA	0.76 (0.64, 0.90)/7	0.77 (0.65, 0.88)
	QUEXR300 vs QUEIR600		1.11 (0.89, 1.35)
	QUEXR300 vs QUEIR300		1.07 (0.86, 1.30)
Response rate	QUEIR600 vs PLA	0.69 (0.62, 0.78)/6	0.69 (0.59, 0.81)
	QUEIR300 vs PLA	0.70 (0.62, 0.79)/6	0.70 (0.59, 0.82)
	QUEIR600 vs QUEIR300	0.99 (0.87, 1,13)	0.99 (0.84, 1.18)
	QUEXR300 vs PLA	0.69 (0.52, 0.91)/6	0.72 (0.58, 0.84)
	QUEXR300 vs QUEIR600		1.04 (0.80, 1.30)
	QUEXR300 vs QUEIR300		1.03 (0.79, 1.29)
Outcome	Comparison	PMA MD (95% CI)	NMA MD (95% CrI)
MADRS	QUEIR600 vs PLA	−4.70 (−6.10, −3.31)	−4.75 (−6.48, −2.99)
	QUEIR300 vs PLA	−4.65 (−6.04, −3.26)	−4.66 (−6.42, −2.94)
	QUEIR600 vs QUEIR300	−0.10 (−1.43, 1.23)	−0.08 (−1.80, 1.63)
	QUEXR300 vs PLA	−3.63 (−5.52, −1.74)	−3.66 (−5.42, −1.90)
	QUEXR300 vs QUEIR600		1.10 (−1.39, 3.48)
	QUEXR300 vs QUEIR300		1.01 (−1.45, 3.51)

95% CI: 95% confidence interval, 95% CrI: 95% credible interval, RR: risk ratio, MADRS: Montgomery Åsberg Depression Rating Scale, MD: mean difference, NMA: network meta-analysis, NNT: number needed to treat, PLA: placebo, PMA: pair-wise meta-analysis, QUEIR600(300): quetiapine immediate release 600 mg/day (300 mg/day), QUEXR300: quetiapine extended release 300 mg/day.

meta-analysis found considerable heterogeneity for somnolence analysis of the QUEXR300 vs. placebo groups (I^2 = 80%, Supplementary appendix 11). Based on this result, we conducted a sensitivity network meta-analysis of the outcome and found that excluding one study in which patients received QUEXR orally once daily at bedtime (Murasaki et al., 2018) from the QUEXR treatment group resulted in no heterogeneity (I^2 = 0%). In the other two QUEXR studies, patients received QUEXR orally once daily in the evening (Li et al., 2016; Suppes et al., 2010). RRs in the sensitivity analysis of the pairwise meta-analysis and network meta-analysis were 3.98 (2.47–6.40) and 3.72 (2.24, 6.61), respectively. Thus, the results of the present study suggest that there may be no differences in the incidence of somnolence with QUEXR300, QUEIR600, or QUEIR300, provided that the patient receives QUEXR300 in the evening.

The study limitations firstly include differences in the characteristics of the patients included in the analyzed studies, including geographical location, race, and ethnicity. Secondly, all studies included in the analysis were industry sponsored, and the possibility of sponsorship bias should be considered when interpreting our results (Higgins and Green, 2011). Thirdly, the small number of studies included prevented the proper use of a funnel plot to estimate potential publication bias as this method is generally used only when ten or more studies are included. Finally, all the included trials had a short duration. Long-term studies will aid in determining differences in the metabolic outcomes of QUEXR and QUEIR.

In conclusion, QUEXR300, QUEIR600, and QUEIR300 were equally effective for the treatment of bipolar depression. However, they were also associated with a greater risk of extrapyramidal symptoms, dry mouth, somnolence, constipation, and increased body weight than placebo. QUEIR600 seemed to be poorly tolerated compared with the other agents. QUEIR300 increased blood HbA1c levels compared with placebo, and patients taking QUEXR300 had an increased risk of fatigue compared with those taking placebo. A long-term study is required to investigate differences in the metabolic outcomes of QUEXR and QUEIR.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study. We have had the following interests within the past 3 years.

Dr. Kishi has received speaker's honoraria from Daiichi Sankyo, Dainippon Sumitomo, Eisai, Janssen, Otsuka, Meiji, MSD, Yoshitomi, and Tanabe-Mitsubishi and has received a Health Labour Sciences Research Grant, Grant-in-Aid for Scientific Research (C) and a Fujita Health University School of Medicine research grant.

Dr. Ikuta received speaker's honoraria from Eli Lilly, Daiichi Sankyo, and Dainippon Sumitomo and is a consultant for Dainippon Sumitomo.

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Contributors

Dr. Kishi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design, Analysis and interpretation of data: Kishi.
Statistical analysis: Kishi and Ikuta.
Acquisition of data: Kishi, Sakuma and Matsuda.
Drafting of the manuscript: All authors.
Study supervision: Iwata.

Role of the funding source

None.

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Table 3
Safety outcomes.

Outcome	Comparison	PMA RR (95% CI)/NNH	NMA RR (95% CrI)
All cause discontinuation	QUEIR600 vs PLA	1.05 (0.86, 1.29)	1.05 (0.84, 1.29)
	QUEIR300 vs PLA	0.93 (0.78, 1.11)	0.93 (0.74, 1.16)
	QUEIR600 vs QUEIR300	1.12 (0.97, 1.30)	1.12 (0.91, 1.38)
	QUEXR300 vs PLA	0.94 (0.70, 1.27)	0.93 (0.71, 1.22)
	QUEXR300 vs QUEIR600		0.89 (0.63, 1.27)
	QUEXR300 vs QUEIR300		1.00 (0.70, 1.44)
Discontinuation due to adverse events	QUEIR600 vs PLA	2.36 (1.33, 4.19)/11	2.25 (1.32, 4.01)
	QUEIR300 vs PLA	1.61 (0.94, 2.76)	1.56 (0.90, 2.78)
	QUEIR600 vs QUEIR300	1.46 (1.14, 1.87)/25	1.45 (0.88, 2.41)
	QUEXR300 vs PLA	2.10 (0.85, 5.23)	1.89 (1.00, 3.88)
	QUEXR300 vs QUEIR600		0.84 (0.36, 2.14)
	QUEXR300 vs QUEIR300		1.21 (0.52, 3.06)
Treatment-emergent mania	QUEIR600 vs PLA	0.57 (0.33, 0.98)/ns	0.55 (0.23, 1.41)
	QUEIR300 vs PLA	0.63 (0.20, 2.06)	0.56 (0.24, 1.38)
	QUEIR600 vs QUEIR300	1.01 (0.48, 2.12)	0.99 (0.41, 2.47)
	QUEXR300 vs PLA	0.55 (0.25, 1.23)	0.41 (0.12, 1.21)
	QUEXR300 vs QUEIR600		0.73 (0.15, 2.87)
	QUEXR300 vs QUEIR300		0.72 (0.15, 2.90)
Suicide–related symptoms	QUEIR600 vs PLA	0.58 (0.23, 1.47)	0.45 (0.16, 1.32)
	QUEIR300 vs PLA	0.84 (0.36, 1.96)	0.67 (0.25, 1.91)
	QUEIR600 vs QUEIR300	0.68 (0.29, 1.59)	0.66 (0.23, 2.01)
	QUEXR300 vs PLA	0.75 (0.25, 2.29)	0.46 (0.11, 1.45)
	QUEXR300 vs QUEIR600		1.03 (0.17, 4.78)
	QUEXR300 vs QUEIR300		0.68 (0.12, 3.03)
Extrapyramidal symptoms	QUEIR600 vs PLA	2.31 (1.41, 3.78)/20	2.12 (1.28, 3.73)
	QUEIR300 vs PLA	2.07 (1.29, 3.30)/25	1.83 (1.07, 3.20)
	QUEIR600 vs QUEIR300	1.16 (0.84, 1.59)	1.16 (0.76, 1.80)
	QUEXR300 vs PLA	3.40 (1.58, 7.33)/17	2.88 (1.29, 6.98)
	QUEXR300 vs QUEIR600		1.34 (0.51, 3.70)
	QUEXR300 vs QUEIR300		1.56 (0.59, 4.35)
Dry mouth	QUEIR600 vs PLA	4.20 (2.51, 7.03)/4	3.75 (2.59, 6.02)
	QUEIR300 vs PLA	4.09 (2.27, 7.37)/5	3.58 (2.46, 5.70)
	QUEIR600 vs QUEIR300	1.05 (0.91, 1.20)	1.05 (0.75, 1.47)
	QUEXR300 vs PLA	5.28 (2.84, 9.76)/5	4.99 (2.95, 8.51)
	QUEXR300 vs QUEIR600		1.33 (0.65, 2.54)
	QUEXR300 vs QUEIR300		1.40 (0.68, 2.67)
Outcome	Comparison	PMA RR (95% CI)/NNH	NMA RR (95% CrI)
Dizziness	QUEIR600 vs PLA	2.62 (1.85, 3.70)/11	2.42 (1.69, 3.58)
	QUEIR300 vs PLA	2.11 (1.48, 3.02)/14	1.97 (1.38, 2.96)
	QUEIR600 vs QUEIR300	1.23 (0.97, 1.56)	1.23 (0.93, 1.61)
	QUEXR300 vs PLA	1.60 (1.05, 2.42)/ns	1.51 (0.96, 2.37)
	QUEXR300 vs QUEIR600		0.63 (0.35, 1.11)
	QUEXR300 vs QUEIR300		0.77 (0.43, 1.37)
Somnolence	QUEIR600 vs PLA	3.55 (2.24, 5.63)/6	3.39 (1.99, 5.90)
	QUEIR300 vs PLA	3.73 (2.46, 5.68)/6	3.58 (2.10, 6.14)
	QUEIR600 vs QUEIR300	0.95 (0.80, 1.13)	0.95 (0.58, 1.53)
	QUEXR300 vs PLA	6.52 (2.39, 17.8)/4	6.02 (3.24, 11.5)
	QUEXR300 vs QUEIR600		1.78 (0.78, 4.07)
	QUEXR300 vs QUEIR300		1.69 (0.76, 3.98)
Fatigue	QUEIR600 vs PLA	1.65 (1.08, 2.54)/25	1.53 (0.93, 2.62)
	QUEIR300 vs PLA	1.34 (0.85, 2.09)	1.25 (0.74, 2.14)
	QUEIR600 vs QUEIR300	1.23 (0.86, 1.77)	1.24 (0.76, 2.01)
	QUEXR300 vs PLA	4.94 (2.20, 11.1)/17	3.76 (1.83, 8.43)
	QUEXR300 vs QUEIR600		2.44 (1.00, 6.44)
	QUEXR300 vs QUEIR300		3.00 (1.21, 8.02)
Constipation	QUEIR600 vs PLA	3.21 (1.93, 5.35)/14	2.81 (1.67, 5.18)
	QUEIR300 vs PLA	2.66 (1.58, 4.46)/25	2.15 (1.27, 3.96)
	QUEIR600 vs QUEIR300	1.29 (0.94, 1.78)	1.31 (0.84, 2.05)
	QUEXR300 vs PLA	2.70 (1.09, 6.66)/17	2.26 (1.20, 4.36)
	QUEXR300 vs QUEIR600		0.80 (0.34, 1.87)
	QUEXR300 vs QUEIR300		1.04 (0.43, 2.51)
≥7% weight gain	QUEIR600 vs PLA	3.08 (1.78, 5.35)/17	2.60 (1.49, 4.87)
	QUEIR300 vs PLA	2.09 (1.15, 3.81)/ns	1.80 (0.98, 3.30)
	QUEIR600 vs QUEIR300	1.41 (0.98, 2.02)	1.45 (0.92, 2.31)
	QUEXR300 vs PLA	4.45 (1.97, 10.0)/17	3.50 (1.67, 7.95)
	QUEXR300 vs QUEIR600		1.35 (0.50, 3.64)
	QUEXR300 vs QUEIR300		1.96 (0.75, 5.35)
Outcome	Comparison	PMA MD (95% CI)	NMA MD (95% CrI)

(*continued on next page*)

Table 3 (*continued*)

Outcome	Comparison	PMA RR (95% CI)/NNH	NMA RR (95% CrI)
Body weight	QUEIR600 vs PLA	1.30 (0.98, 1.63)	1.30 (0.89, 1.70)
	QUEIR300 vs PLA	0.98 (0.67, 1.30)	0.97 (0.58, 1.36)
	QUEIR600 vs QUEIR300	0.32 (0.02, 0.62)	0.33 (−0.05, 0.70)
	QUEXR300 vs PLA	1.47 (1.08, 1.86)	1.47 (0.95, 1.98)
	QUEXR300 vs QUEIR600		0.18 (−0.46, 0.84)
	QUEXR300 vs QUEIR300		0.50 (−0.14, 1.15)
Blood glucose	QUEIR600 vs PLA	1.37 (−0.84, 3.58)	1.54 (−0.76, 3.95)
	QUEIR300 vs PLA	1.21 (−0.96, 3.38)	1.08 (−1.25, 3.48)
	QUEIR600 vs QUEIR300	0.44 (−2.13, 3.01)	0.46 (−1.80, 2.66)
	QUEXR300 vs PLA	−0.06 (−0.22, 0.11)	0.001 (−1.21. 2.03)
	QUEXR300 vs QUEIR600		−1.46 (−4.13, 1.55)
	QUEXR300 vs QUEIR300		−0.97 (−3.70, 2.02)
Blood HbA1c	QUEIR600 vs PLA	0.05 (0.01, 0.10)	0.05 (−0.02, 0.13)
	QUEIR300 vs PLA	0.08 (0.03, 0.13)	0.08 (0.003, 0.16)
	QUEIR600 vs QUEIR300	−0.03 (−0.08, 0.03)	−0.02 (−0.10, 0.05)
	QUEXR300 vs PLA	0.02 (−0.02. 0.06)	0.02 (−0.04, 0.08)
	QUEXR300 vs QUEIR600		−0.04 (−0.13, 0.06)
	QUEXR300 vs QUEIR300		−0.06 (−0.16, 0.03)
Blood insulin	QUEIR600 vs PLA	12.7 (−9.93, 35.4)	12.9 (−19.4, 46.3)
	QUEIR300 vs PLA	7.03 (−18.0, 32.1)	4.31 (−28.8, 37.1)
	QUEIR600 vs QUEIR300	9.60 (−22.8, 42.0)	8.53 (−22.2, 40.6)
	QUEXR300 vs PLA	3.98 (−13.9, 21.8)	2.70 (−19.4, 35.4)
	QUEXR300 vs QUEIR600		−8.79 (−48.5, 37.2)
	QUEXR300 vs QUEIR300		0.37 (−39.0, 47.0)
Blood triglyceride	QUEIR600 vs PLA	11.3 (−6.25, 28.8)	11.3 (−20.6, 44.6)
	QUEIR300 vs PLA	9.09 (−7.42, 25.6)	8.99 (−23.9, 42.5)
	QUEIR600 vs QUEIR300	3.25 (−8.66, 15.2)	2.50 (−29.3, 33.5)
	QUEXR300 vs PLA	15.8 (−17.2, 48.8)	13.5 (−14.7, 45.8)
	QUEXR300 vs QUEIR600		1.86 (−41.1, 48.2)
	QUEXR300 vs QUEIR300		4.54 (−38.0, 50.5)
Blood total cholesterol	QUEIR600 vs PLA	2.01 (−6.96, 11.0)	1.97 (−7.77, 11.8)
	QUEIR300 vs PLA	−1.59 (−10.9, 7.74)	−1.72 (−11.3, 8.28)
	QUEIR600 vs QUEIR300	3.49 (−1.07, 8.05)	3.65 (−5.72, 13.0)
	QUEXR300 vs PLA	4.14 (−4.61, 12.9)	3.65 (−4.68, 13.1)
	QUEXR300 vs QUEIR600		1.82 (−11.0, 15.2)
	QUEXR300 vs QUEIR300		5.38 (−7.29, 18.6)
Outcome	Comparison	PMA MD (95% CI)	NMA MD (95% CrI)
Blood HDL cholesterol	QUEIR600 vs PLA	−1.02 (−2.53, 0.49)	−1.05 (−3.01, 0.94)
	QUEIR300 vs PLA	−1.21 (−2.82, 0.40)	−1.17 (−3.01, 0.76)
	QUEIR600 vs QUEIR300	0.13 (−1.20, 1.46)	0.12 (−1.67, 1.88)
	QUEXR300 vs PLA	−0.00 (−0.07, 0.07)	−0.04 (−1.59, 1.27)
	QUEXR300 vs QUEIR600		0.97 (−1.50, 3.26)
	QUEXR300 vs QUEIR300		1.09 (−1.29, 3.36)
Blood LDL cholesterol	QUEIR600 vs PLA	0.49 (−4.02, 4.99)	0.49 (−5.93, 7.04)
	QUEIR300 vs PLA	−2.06 (−7.39, 3.28)	−2.06 (−8.44, 4.40)
	QUEIR600 vs QUEIR300	2.46 (−1.59, 6.51)	2.51 (−3.57, 8.68)
	QUEXR300 vs PLA	2.34 (−2.98, 7.66)	1.77 (−2.71, 7.67)
	QUEXR300 vs QUEIR600		1.40 (−6.29, 1.00)
	QUEXR300 vs QUEIR300		3.93 (−3.97, 12.7)

95% CI: 95% confidence interval, 95% CrI: 95% credible interval, RR: risk ratio, MD: mean difference, NMA: network meta-analysis, NNH: number needed to harm, ns: not significant, PLA: placebo, PMA: pair-wise meta-analysis, QUEIR600(300): quetiapine immediate release 600 mg/day (300 mg/day), QUEXR300: quetiapine extended release 300 mg/day.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.05.020.

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